Clinical Infectious Diseases

MAJOR ARTICLE

Causes and Clinical Features of Childhood Encephalitis: A Multicenter, Prospective Cohort Study

Philip N. Britton,[1,2,3] Russell C. Dale,[1,4] Christopher C. Blyth,[5,6,7] Julia E. Clark,[8,9] Nigel Crawford,[10,11] Helen Marshall,[12,13] Elizabeth J. Elliott,[1,14] Kristine Mac artney,[1,3,15] Robert Booy,[1,2,3,15] and Cheryl A. Jones[2,10,11]; for the Australian Childhood Encephalitis Study Investigators and the Paediatric Active Enhanced Disease Surveillance Network

[1]Discipline of Child and Adolescent Health, Sydney Medical School, [2]Marie Bashir Institute of Infectious Diseases and Biosecurity Institute, University of Sydney, and Departments of [3]Infectious Diseases and Microbiology, and [4]Neurology, Children's Hospital at Westmead, New South Wales, [5]Perth Children's Hospital, [6]Telethon Kids Institute and School of Medicine, University of Western Australia, and [7]PathWest Laboratory Medicine Western Australia and Queen Elizabeth II Medical Centre, Nedlands, Perth, Western Australia; [8]Children's Health Queensland, and [9]School of Clinical Medicine, University of Queensland, Brisbane, [10]Murdoch Children's Research Institute and Royal Children's Hospital, and [11]University of Melbourne, Victoria, [12]Women's and Children's Hospital, and [13]Robinson Research Institute, University of Adelaide, South Australia, and [14]Australian Paediatric Surveillance Unit, and [15]National Centre for Immunisation Research and Surveillance, Westmead, New South Wales, Australia

(See the Editorial Commentary by Glaser and Bloch on pages 2527–9.)

Background. We aimed to determine the contemporary causes, clinical features, and short-term outcome of encephalitis in Australian children.

Methods. We prospectively identified children (≤14 years of age) admitted with suspected encephalitis at 5 major pediatric hospitals nationally between May 2013 and December 2016 using the Paediatric Active Enhanced Disease Surveillance (PAEDS) Network. A multidisciplinary expert panel reviewed cases and categorized them using published definitions. Confirmed encephalitis cases were categorized into etiologic subgroups.

Results. From 526 cases of suspected encephalitis, 287 children met criteria for confirmed encephalitis: 57% (95% confidence interval [CI], 52%–63%) had infectious causes, 10% enterovirus, 10% parechovirus, 8% bacterial meningoencephalitis, 6% influenza, 6% herpes simplex virus (HSV), and 6% *Mycoplasma pneumoniae*; 25% (95% CI, 20%–30%) had immune-mediated encephalitis, 18% acute disseminated encephalomyelitis, and 6% anti-*N*-methyl-D-aspartate receptor encephalitis; and 17% (95% CI, 13%–21%) had an unknown cause. Infectious encephalitis occurred in younger children (median age, 1.7 years [interquartile range {IQR}, 0.1–6.9]) compared with immune-mediated encephalitis (median age, 7.6 years [IQR, 4.6–12.4]). Varicella zoster virus encephalitis was infrequent following high vaccination coverage since 2007. Thirteen children (5%) died: 11 with infectious causes (2 influenza; 2 human herpesvirus 6; 2 group B *Streptococcus*; 2 *Streptococcus pneumoniae*; 1 HSV; 1 parechovirus; 1 enterovirus) and 2 with no cause identified. Twenty-seven percent (95% CI, 21%–31%) of children showed moderate to severe neurological sequelae at discharge.

Conclusions. Epidemic viral infections predominated as causes of childhood encephalitis in Australia. The leading causes include vaccine-preventable diseases. There were significant differences in age, clinical features, and outcome among leading causes. Mortality or short-term neurological morbidity occurred in one-third of cases.

Keywords. encephalitis; child; infant; neonate; epidemiology.

Encephalitis, particularly from infectious diseases, is recognized as causing a considerable disease burden [1]. Improving its diagnosis and management is a major challenge [2]. Encephalitis occurs most commonly in children, yet children make up a minority of cases in large prospective epidemiological studies performed since 1998 [3–5]. There are few prospective, multicenter pediatric studies and none since publication of an international case definition [1]. Retrospective or single-center studies are likely hampered by sampling biases when assessing the etiological spectrum and severity of disease [1], and there are limitations to using administrative datasets [6–8]. Furthermore, the impact of comprehensive vaccination programs and the increasing recognition of antibody-mediated encephalitides have altered epidemiology in high-income settings [1, 6].

We therefore sought to undertake a national, prospective study of Australian children hospitalized with encephalitis. We aimed to describe the etiological spectrum (including infectious, immune-mediated, and unknown causes), compare the clinical features of known causes with that of unknown cause, and investigate risk factors for short-term adverse outcomes.

METHODS

The Australian Childhood Encephalitis (ACE) study is a prospective cohort captured using active surveillance in

Received 20 March 2019; editorial decision 15 June 2019; accepted 24 July 2019; published online August 1, 2019.

Correspondence: P. N. Britton, Discipline of Child and Adolescent Health, Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia (philip.britton@health.nsw.gov.au).

Clinical Infectious Diseases® 2020;70(12):2517–26

DOI: 10.1093/cid/ciz685

partnership with the Paediatric Active Enhanced Disease Surveillance (PAEDS) network [9]. The study methodology and evaluation of a pilot study has been recently described [10]. The study commenced in 2013 in New South Wales and then from 2014 extended to include 5 tertiary pediatric hospitals (www.paeds.edu.au). For additional methodological detail, see the Supplementary Materials.

For this analysis, all suspected encephalitis cases were extracted from their inclusion in surveillance until 31 December 2016. The investigation and management of individual cases was at the discretion of treating physicians. Individual case data were reviewed by an expert pediatric panel. Cases were categorized as "confirmed encephalitis" or "not encephalitis" [10], and further categorized into etiological groups using Granerod et al's criteria [11]. We re-reviewed magnetic resonance imaging (MRI) scans from children provisionally categorized as having acute disseminated encephalomyelitis (ADEM) [12, 13]. Cases were allocated to 1 of 3 etiological groups (infectious, immune-mediated, and unknown) for comparative analyses.

Demographics, clinical data, and etiology were compared between 2 outcome categories ("good recovery" = Glasgow Outcome Score [GOS] of 5; "death or neurological morbidity" = GOS of 1 [death] + GOS of 2–4) using multivariable logistic regression analysis including cases with complete data.

RESULTS

Population

From 2013 to 2016, we identified 526 children aged ≤14 years with suspected encephalitis at 5 hospitals. Of these, 287 children were categorized as having confirmed encephalitis (55% of suspected cases; Figure 1). The 239 cases categorized as "not encephalitis" included both infectious and immune-mediated central nervous system (CNS) diseases (Figure 1).

The demographic characteristics of those with confirmed childhood encephalitis were compared across the 3 major etiological subgroups (Supplementary Table 1 and Figure 2). Overall, 56% of cases were male; with no significant difference between groups. The median age of children with infectious encephalitis (1.7 years [interquartile range {IQR}, 0.09–6.9]) was significantly ($P < .001$) younger than children with immune-mediated encephalitis (7.1 years [IQR, 2.4–9.8]) (Supplementary Table 1 and Figure 2). Most infectious encephalitis cases occurred in children aged ≤4 years (70%; with 43% aged <1 year); only 26% of immune-mediated encephalitis occurred in this age range. Less than 5% of children had preexisting neurological disease or immunocompromise. There were no geographic differences in the distribution of etiological subgroups (Supplementary Table 1).

Etiology

Of confirmed encephalitis cases, 57% (95% confidence interval [CI], 52%–63%; n = 165) had infectious causes, 25% (95% CI, 20%–30%; n = 73) immune-mediated causes, and 17% (95% CI, 13%–21%; n = 49) an unknown cause (Table 1). Among infectious encephalitis, the leading causes were parechovirus (10%; n = 29), enteroviruses (10%; n = 29), influenza (6%; n = 18), herpes simplex virus (HSV) (6%; n = 17), and *Mycoplasma pneumoniae* (6%; n = 16). Of the 8% (n = 22) with bacterial meningoencephalitis, *Streptococcus pneumoniae* and group B *Streptococcus* (GBS) were predominant, with single cases caused by other bacteria (Table 1).

These leading causes of infectious encephalitis were all "confirmed" or "probable" causes using the Granerod et al criteria except for influenza, enteroviruses, and *M. pneumoniae* (Table 1). A small number of cases were associated ("probable" or "possible" cause) with Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), Murray Valley encephalitis virus (MVEV), adenovirus, and respiratory syncytial virus (RSV). Other infectious causes occurred as single cases and were "possible" causes using the Granerod et al criteria.

Among the immune-mediated encephalitis cases were 2 predominant causes (Table 1): ADEM (18%; n = 51) and anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDAR) (6%; n = 17). We identified 1 case of anti-glutamic acid decarboxylase antibody encephalitis. Four cases were categorized as immune-mediated "other" (all relapsing inflammatory brain disease but not juvenile-onset multiple sclerosis; Table 1). The causes among young infants aged <1 year and cases with immunocompromise are detailed in Supplementary Tables 2 and 3.

There were 2 patients with of HSV encephalitis who subsequently (≤4 weeks) developed anti-NMDAR encephalitis: 12% (95% CI, 8%–16%; n = 2/17) of all HSV cases and 15% (2/13) of nonneonatal cases. These were categorized as infectious encephalitis, although noted as additional immune-mediated cases (Table 1). Of the ADEM cases, 12 (24%) showed evidence of possible associated infection: 3 with serological evidence of acute *M. pneumoniae*, 3 with serological evidence of recent EBV, and 6 with polymerase chain reaction (PCR) detection of a virus from a nonsterile site (2 enterovirus, 1 adenovirus, 1 RSV, and 2 with multiple pathogens).

The clinical features of the cases are shown in Supplementary Table 2. No feature was present in all children. Those reported most frequently were lethargy (90%), fever (74%), altered personality/behavior (73%), seizure with loss of consciousness (45%), reduced GCS (43%), and a focal neurological sign (45%). If tested, abnormality was found most frequently on electroencephalography (EEG) (83%), followed by MRI (73%), then cerebrospinal fluid (CSF) (pleocytosis in 66%). No specific clinical features were overrepresented in the unknown encephalitis group (Supplementary Table 4). Furthermore, there were no features on exposure history overrepresented in the unknown encephalitis group (Supplementary Table 5). Overall, etiological testing among cases of childhood encephalitis was incomplete compared with national guidelines published after study commencement [14] (see Supplementary Table 6).

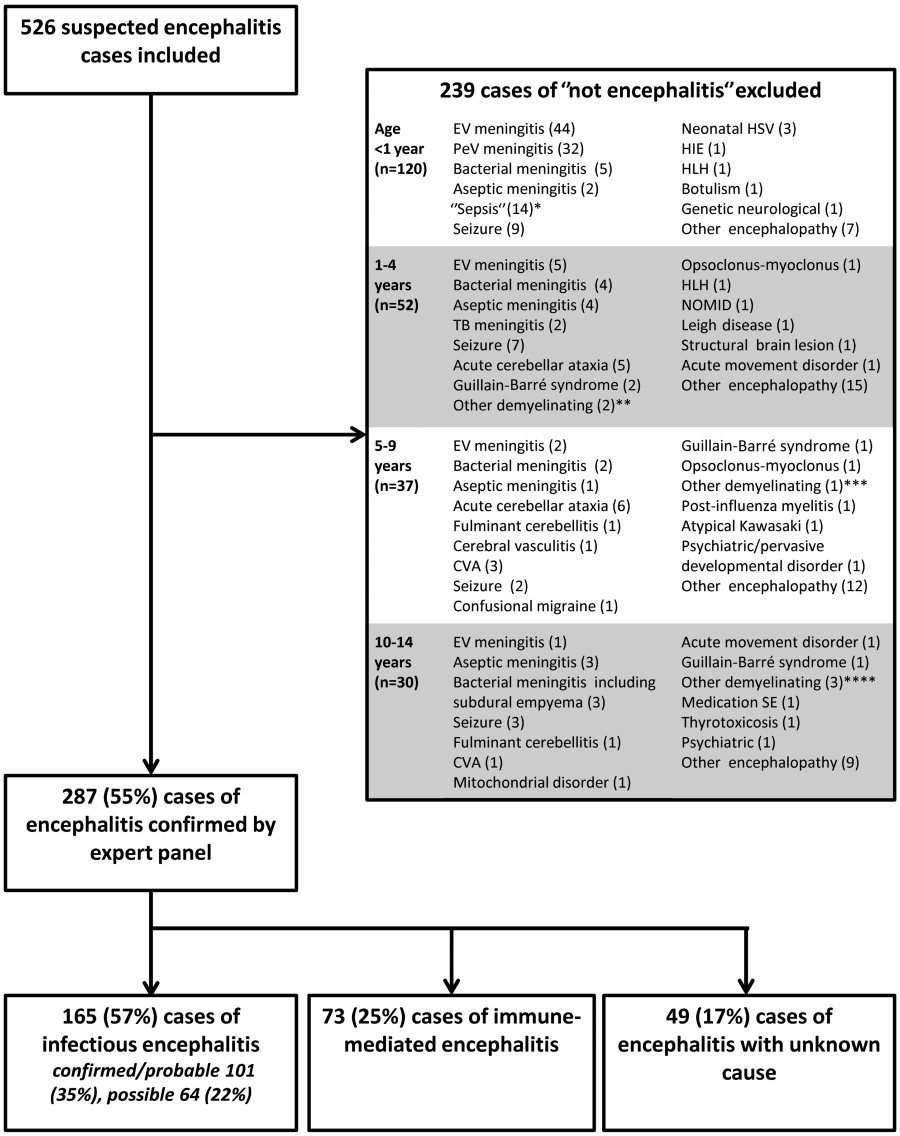

Figure 1. Flowchart showing categorization of childhood (age ≤14 years) suspected encephalitis cases identified by the Australian Childhood Encephalitis study, 2013–2016. The 3 cases categorized as neonatal herpes simplex virus (HSV) were babies at risk, investigated early, and had HSV DNA detected in cerebrospinal fluid without clinical features of encephalitis. In the absence of early investigation and treatment, these cases may have progressed. *One *Neisseria meningitidis*, 9 parechovirus (PeV), 2 enterovirus (EV), 1 EV + PeV, 1 nil cause. **One clinically isolated syndrome (CIS), 1 probable NMO. ***One CIS. ****Two CIS, 1 postradiotherapy demyelination. Abbreviations: CVA, cerebrovascular accident; HIE, hypoxic ischemic encephalopathy; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; NMO, neuromyelitis optica; NOMID, neonatal onset multisystem inflammatory disease; SE, side effect; TB, tuberculosis.

Leading Causes—Epidemiology and Clinical Features

Eight specific causes accounted for more than two-thirds (69%) of all confirmed encephalitis cases: 6 infectious (enteroviruses, parechovirus, HSV, influenza, *M. pneumoniae*, "bacterial" meningoencephalitis) and 2 immune-mediated (ADEM and anti-NMDAR). Among the leading infectious causes, many occurred in association with defined epidemic periods (Supplementary Figure 1) [15–19]. Five of 29 (17%) enteroviral cases occurred during the EVA71 epidemic in 2013 [15]. Other enteroviral cases occurred in late autumn and spring/early summer. All parechovirus cases occurred during 2 epidemics in 2013–2014 and 2015–2016 [16, 17, 20]. Influenza-associated encephalitis only occurred during the southern hemisphere influenza season [18]. A cluster of *M. pneumoniae* encephalitis occurred in New South Wales between July and October 2015 [19]. HSV encephalitis was an exception, occurring sporadically across the surveillance period. There was no clear clustering or seasonality among ADEM cases (Supplementary Figure 1).

The clinical features, severity, and outcome of these leading infectious and immune-mediated causes of encephalitis

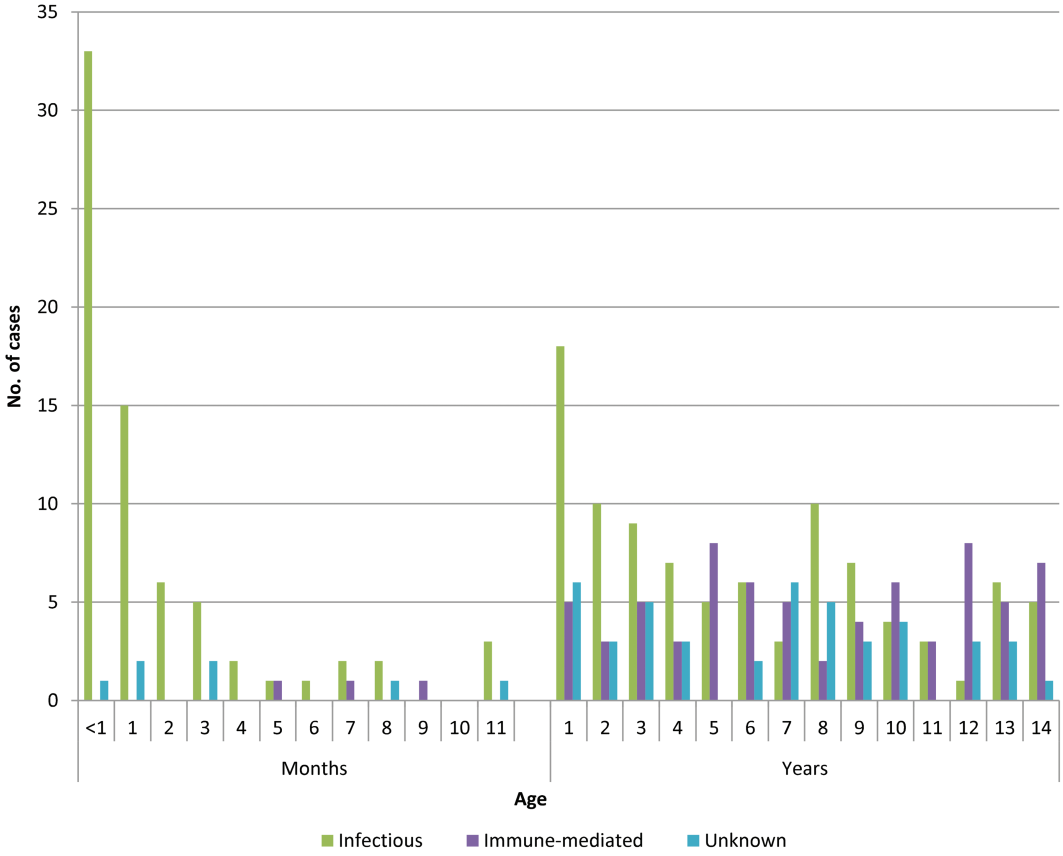

Figure 2. Bar chart showing the age distribution of cases of childhood (age ≤14 years) encephalitis identified by the Australian Childhood Encephalitis study, 2013–2016.

are shown in Table 2. Age differed significantly. All cases of parechovirus encephalitis occurred in children aged <1 year (median age, 0.06 years). Enteroviruses, HSV, and influenza encephalitis occurred primarily in preschool-aged children (75%, 73%, and 80% aged ≤4 years, respectively). An exception among infectious causes was *M. pneumoniae*–associated encephalitis (median age, 9.1 years). Immune-mediated encephalitis occurred in older children; ADEM and anti-NMDAR occurred in children with median ages of 6.8 and 10.1 years, respectively (Table 2). There were significant differences in the core features of encephalitis among these leading causes (Table 2).

Outcome at Discharge

Disease severity and outcomes are shown in Supplementary Table 7. Intensive care unit (ICU) admission occurred in 49%, and was more frequent in infectious and unknown causes than immune-mediated encephalitis. Median length of hospitalization was 11 days, with a higher proportion of immune-mediated cases requiring prolonged hospitalization (>14 days; Supplementary Table 5). Fourteen children died, 13 directly attributable to encephalitis (13/287; case fatality proportion 5% [95% CI, 2%–7%]); 11 from infectious encephalitis (2 influenza, 2 HHV-6, 2 GBS, 2 *S. pneumoniae*, 1 HSV, 1 parechovirus, 1 enterovirus) and 2 with encephalitis of unknown cause. Twenty-seven percent of children showed moderate to severe neurodisability at discharge from hospital (GOS ≤ 4).

Risk Factors for Adverse Outcome

Several factors were associated with adverse outcome when stratified by GOS at discharge (Table 3; Supplementary Table 8). Seizure with loss of consciousness (odds ratio [OR], 2.4), Glasgow Coma Scale (GCS) score <13 (OR, 3.5), abnormal EEG (OR, 2.9), and ICU admission (OR, 3.3) were all associated with neurological morbidity or death. Having encephalitis caused by bacterial infection (OR, 2.9), HSV (OR, 6.0), influenza (OR, 4.2), anti-NMDAR (OR, 4.7), or ADEM (OR, 2.7) was associated with adverse outcome (Table 3). In a multivariable logistic regression model, the following factors remained statistically significantly associated with adverse outcome: HSV (OR, 20.3), influenza (OR, 12.1), anti-NMDAR (OR, 24.5) or ADEM (OR, 11.5), and the clinical features of reduced GCS (OR, 2.9) and admission to ICU (OR, 6.5) (Table 3).

DISCUSSION

The Australian Childhood Encephalitis study is the largest prospective cohort of all-cause childhood encephalitis in the world, and the first study of its kind in the Southern Hemisphere. It is

Table 1. Causes of Childhood (Age ≤14 Years) Encephalitis Identified by the Australian Childhood Encephalitis Study, 2013–2015

Cause	Confirmed/Probable[a]	Possible	Total No. (%) or No. (% [95% CI])
Suspected encephalitis	…	…	526
Confirmed encephalitis (% suspected encephalitis)	…	…	287 (55)
Infectious	101 (35 [30–41])	64 (22 [18–27])	165 (57 [52–63])
Parechovirus	28	1	29 (10 [7–14])
Enterovirus	17	12	29 (10 [7–13])
"Bacterial"[b] meningoencephalitis	22	…	22 (8 [5–11])
Influenza	…	18	18 (6 [3–9])
HSV	17	…	17 (6 [3–9])
Mycoplasma pneumoniae	12	4	16 (6 [3–8])
HHV-6	1	2	3 (1)
EBV	2	…	2 (1)
MVEV	1	1	2 (1)
CMV	1	…	1 (<1)
RSV	…	3	3 (1)
Adenovirus	…	2	2 (1)
VZV	…	1	1 (<1)
HMPV	…	1	1 (<1)
Norovirus	…	1	1 (<1)
Rotavirus	…	1	1 (<1)
Cryptococcus species	…	1	1 (<1)
Toxocariasis	…	1	1 (<1)
Mixed[c]	…	15	15 (5 [3–8])
Immune-mediated	73	…	73 (25 [20–30])
ADEM	51	…	51 (18 [13–22])
Anti-NMDAR	17 (2)[d]	…	17 (6 [3–9])
Anti-GAD	1	…	1 (<1)
Other[e]	4	…	4 (1)
Unknown	49	…	49 (17 [13–21])

Abbreviations: ADEM, acute disseminated encephalomyelitis; CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GAD, glutamic acid decarboxylase; HHV-6, human herpesvirus type 6; HMPV, human metapneumovirus; HSV, herpes simplex virus; MVEV, Murray Valley encephalitis virus; NMDAR, *N*-methyl-D-aspartate receptor; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

[a]All cases of enterovirus, parechovirus, and HSV encephalitis were confirmed (by detection of viral nucleic acid in cerebrospinal fluid [CSF]). All but 3 cases of bacterial meningoencephalitis were confirmed (cultured from CSF); in 3 a blood culture specimen was positive in addition to CSF, clinical, or imaging findings of meningitis. The CMV case was confirmed (posttransplant, CMV polymerase chain reaction [PCR] positive in CSF and blood with positive immunoglobulin M [IgM]). All mycoplasma cases were probable (serum IgM positive). The HHV-6 (posttransplant encephalitis with detection of viral nucleic acid in CSF), MVEV (1 IgM positive AND immunoglobulin G positive in acute sera; 1 seroconversion), and CMV cases in this column were probable. One EBV case was confirmed (detection of viral nucleic acid in CSF and serology suggesting acute infection) and 1 was probable (detection of viral nucleic acid in CSF only).

[b]*Streptococcus pneumoniae* (n = 8); group B *Streptococcus* (*S. agalactiae*) (n = 7); *Neisseria meningitidis* (n = 1); group A *Streptococcus* (*S. pyogenes*) (n = 1); *Escherichia coli* (n = 1); *Citrobacter freundii* (n = 1); *Enterobacter cloacae* (n = 1); *Listeria monocytogenes* (n = 1); *Salmonella* species (n = 1).

[c]These included multiple viruses identified using multiplex PCR testing on respiratory specimens, or 1 virus detected in combination with positive serology for *Mycoplasma pneumoniae*. ^Probable autoinflammatory central nervous system disorder (n = 1); antimyelin oligodendrocyte-associated encephalitis (n = 2); relapsing demyelinating disorder not otherwise specified (n = 1).

[d]These 2 cases occurred following (≤4 weeks) confirmed HSV encephalitis. The cases have been categorized as cases of HSV encephalitis in this table and are not included in the proportional contribution of anti-NMDAR encephalitis.

[e]Where subtyping was performed, 8 were HSV-1; 3 were HSV-2.

distinct in including children from birth, not only those aged >6 months [1]. In contrast to the larger California Encephalitis Project cohort, it recruited all children hospitalized with syndromes suggestive of encephalitis, not selected cases referred for further investigation [3, 21]. The cohort was recruited using active hospital-based surveillance—the PAEDS Network—which, although not population-based, is nationally representative, including the largest pediatric hospitals in the most populous Australian states [22].

We have definitively shown that the leading causes of childhood encephalitis in Australia are enteroviruses, parechovirus, HSV, influenza, *M. pneumoniae*, *Streptococcus* species, ADEM, and anti-NMDAR. By comparison, several large prospective cohort studies in predominantly adults from high-income countries showed the leading causes of adult encephalitis to be HSV, varicella zoster virus (VZV), *Mycobacterium tuberculosis*, *Listeria monocytogenes*, and anti-NMDAR (Supplementary Table 9) [3–5]. In these studies, enteroviruses, EBV, *M. pneumoniae*, and ADEM were more frequent in children [3, 5]. Furthermore, we have shown that age was a key determinant of cause across childhood. Parechovirus, enteroviruses, and bacterial meningoencephalitis predominate in young infants. In older infants and toddlers, enteroviruses, influenza, and HSV predominate. Among children and young adolescents, ADEM,

Table 2. Demographics, Clinical Features, Disease Severity, and Outcome of the Leading (n ≥ 10) Causes of Childhood (Age ≤14 Years) Encephalitis Identified by the Australian Childhood Encephalitis Study, 2013–2016

Characteristic	Enterovirus (n = 29)	Parechovirus (n = 29)	"Bacterial" (n = 22)	Influenza (n = 18)	HSV (n = 17)	Mycoplasma (n = 16)	ADEM (n = 51)	Anti-NMDAR (n = 17)	*P* Value[a]
Demographics									
Male sex	16 (55)	13 (45)	11 (50)	6 (33)	10 (59)	9 (56)	34 (67)	6 (35)	.19
Median age, y (IQR)	1.8 (0.2–4.3)	0.04 (0.03–0.08)	0.3 (0.07–0.8)	4.0 (1.8–8.4)	1.0 (0.05–8.8)	9.1 (7.6–10.6)	6.8 (3.7–11.2)	10.1 (6.1–13.4)	**< .001**[b,c]
Core features of encephalitis									
Fever	20 (69)	22 (76)	17 (77)	15 (83)	13 (76)	14 (86)	38/49 (78)	4 (23)	**.001**
Seizure with LOC	10 (35)	15 (52)	12 (55)	10/17 (59)	12 (71)	5 (31)	6 (12)	8 (47)	**< .001**[c]
Lethargy	22/27 (82)	27 (93)	20 (91)	18 (100)	14 (82)	16 (100)	47/50 (94)	11 (65)	**.01**
Altered personality/ behavior	17 (59)	22[d] (76)	13/21 (62)	8 (44)	16 (94)	12 (75)	38 (74)	17 (100)	**.002**
GCS score <13[e]	8/18 (44)	3/8 (38)	9/14 (64)	8/14 (57)	8/9 (89)	8/16 (50)	12/44 (27)	2/13 (15)	**.004**
GCS score <9[e]	5/18 (28)	3/8 (38)	3/14 (21)	3/14 (21)	2/9 (22)	2/16 (13)	3/44 (7)	2/13 (15)	.22
Increased CSF WCC	17/28 (61)	2/26 (8)	16/18 (89)	6/15 (40)	13/17 (77)	13 (81)	43/49 (88)	10 (59)	**< .001**[c]
Abnormal MRI[f]	15/25 (60)	23/26 (89)	21 (96)	12 (75)	12 (75)	7/15 (47)	51 (100)	5/16 (31)	**< .001**[c]
Abnormal EEG[f]	14/18 (78)	10/13 (77)	14/14 (100)	7/9 (78)	11/11 (100)	10/12 (83)	13/16 (82)	12/14 (86)	.41
Focal neurological signs									
Cranial nerve abnormalities[e]	1/22 (4)	0/19	1/16 (6)	2/11 (18)	3/14 (21)	0/15	20/46 (44)	5/15 (33)	**< .001**[c]
Limb weakness[e]	6/24 (25)	5/21 (24)	8/18 (44)	9/14 (64)	8/14 (57)	4/14 (29)	35/48 (73)	6/16 (38)	**< .001**[c]
Bladder/bowel dysfunction[e]	1/23 (4)	1/22 (5)	2/15 (13)	3/13 (23)	5/14 (36)	9/16 (56)	29/48 (60)	6/17 (35)	**< .001**[c]
Abnormal movements[e]	7/26 (27)	7/26 (27)	10/21 (48)	3/15 (20)	8/17 (47)	10/16 (63)	20/50 (40)	10/17 (59)	.08
Severity and outcome									
ICU	15 (52)	26 (90)	18 (82)	8 (44)	10 (59)	6 (38)	13 (26)	5 (29)	**< .001**[c]
Death	1 (3)	1 (3)	4 (18)	2 (11)	1 (6)	0	0	0	.02
Median days in hospital (IQR)	7 (4–14)	8 (5–12)	19 (14–44)	9 (4–24)	23 (14–65)	8 (7–12)	8 (5–21)	33 (14–90)	**< .001**[c]
Neurological morbidity at discharge (GOS ≤ 4)[g]	4 (14)	7 (25)	5 (28)	7 (44)	9 (56)	1 (6)	20 (39)	9 (53)	**.005**

Data are presented as no. (%) unless otherwise indicated. Boldfaced P values show significance at an α level of .05.

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EEG, electroencephalogram; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; HSV, herpes simplex virus; ICU, intensive care unit; IQR, interquartile range; LOC, loss of consciousness; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; WCC, white cell count.

[a]Fisher exact test comparing frequency across 8 subgroups unless otherwise specified.

[b]Kruskal-Wallis test.

[c]These *P* values also show significance following Bonferroni adjustment for multiple statistical testing.

[d]In all of these cases, altered behavior was described as excessive irritability.

[e]Up to 40% of cases did not have these data fields completed; reported as a proportion of cases with recorded data. For each data point, the incomplete proportion did not differ significantly among the subgroups.

[f]Reported as a proportion of those in whom the test was performed.

[g]Reported as a proportion of survivors.

Table 3. Statistically Significant Factors Associated With Adverse Outcome (Death or Neurological Morbidity) in a Multivariable Logistic Regression Model Among Cases of Childhood (Age ≤14 Years) Encephalitis Identified by the Australian Childhood Encephalitis Study, 2013–2015

Predictor	Univariate OR (95% CI)	*P* Value	Multivariable aOR (95% CI)[a]	*P* Value
Age, y		**.203**		**.441**
<1	1.0 (.5–2.1)		0.6 (.1–2.4)	
1–4	1.2 (.6–2.5)		1.0 (.3–2.7)	
5–9	0.55 (.25–1.2)		0.5 (.2–1.3)	
≥10	1.0 (ref)		1.0 (ref)	
Clinical features				
Fever	0.62 (.35–1.1)	.11	0.6 (.2–1.4)	ns
Seizure with LOC	2.4 (1.4–4.0)	**.001**	1.1 (.5–2.5)	ns
Altered personality/behavior	1.6 (.88–2.9)	.15	1.6 (.6–4.2)	ns
GCS score <13[b]	3.5 (1.9–6.4)	**<.001**	2.9 (1.1–7.2)	**.03**
Abnormal MRI	2.4 (1.2–4.7)	**.007**	Not entered	
Abnormal EEG	2.9 (1.0–8.2)	**.03**	Not entered	
ICU admission	3.3 (1.9–5.6)	**<.001**	6.5 (2.0–20.8)	**.002**
Specified leading causes		**.001**		**<.001**
Other	1.0 (ref)		1.0 (ref)	
Enterovirus	0.87 (.29–2.6)		1.1 (.2–5.4)	
Parechovirus	1.6 (.60–4.2)		2.6 (.2–21.7)	
Bacterial	2.9 (1.1–7.9)		2.9 (.6–14.2)	
Influenza	4.2 (1.4–12.1)		12.1 (2.2–68)	
HSV	6.0 (2.0–17.9)		20.3 (2.8–151)	
Mycoplasma	0.28 (.03–2.3)		0.32 (.03–3.4)	
ADEM	2.7 (1.2–5.8)		11.5 (3.5–38.2)	
Anti-NMDAR	4.7 (1.6–14.0)		24.5 (4.8–124.5)	

Boldfaced *P* values show significance at an alpha level of .05.

Abbreviations: ADEM, acute disseminated encephalomyelitis; aOR, adjusted odds ratio; CI, confidence interval; EEG, electroencephalogram; GCS, Glasgow Coma Scale; HSV, herpes simplex virus; ICU, intensive care unit; LOC, loss of consciousness; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; ns, not significant; OR, odds ratio.

[a]Variables entered: age, fever, seizure with LOC, altered personality/behavior (GCS score <13), ICU admission, specified leading causes. Model parameters: n = 195 (ie, 92 cases with missing data). Test of model coefficients: χ^2 = 71.525 at 16 degrees of freedom (*P* < .001). Nagelkerke R^2 = 0.428. Hosmer-Lemeshow *P* value = 0.850. Prediction percentage in null model = 67.2%, in test model = 80.0%.

[b]In an alternative model generated using GCS score <9 as a cutoff, multivariable aOR was 3.4 (*P* = .02).

anti-NMDAR, and *M. pneumoniae* predominate. A similar association of age with etiology was shown in a retrospective, single-center cohort from Australia, although influenza was infrequent and parechovirus absent in that study [23]. Location remains significant in determining cause with respect to endemic flaviviruses; 2 of our cases were caused by MVEV, both from Northern Australia. In Asia, Japanese encephalitis virus predominates in childhood encephalitis [24, 25], and in parts of Europe, tickborne encephalitis virus is prominent [26]. Another key finding was that VZV was unexpectedly infrequent as a cause in this cohort. This is likely due to high varicella vaccine coverage and effectiveness in Australia since inclusion in the National Immunisation Program in 2007 [6, 27]. We also note that acute cerebellar ataxia was specifically excluded from encephalitis categorization, although VZV was not implicated even in excluded cases (Figure 1).

Encephalitis is an uncommon and severe disease with protean manifestations. Clinician investigation and management tend to be suboptimal [28, 29]. We have shown significant differences in the clinical features between the leading causes of childhood encephalitis. Few previous studies have compared clinical features between subgroups [23]. Our findings contribute to supporting clinicians in the diagnosis, empiric treatment, and early investigation of suspected encephalitis in children. Furthermore, we have identified that a substantial proportion of infectious encephalitis in Australian children occurred in epidemics. This supports ongoing surveillance, with timely reporting to increase clinician awareness of disease trends, especially in epidemic periods, and support optimal management of children with this serious condition.

We have shown that a putative cause is identifiable in up to 80% of cases of childhood encephalitis (75% if mixed infectious cases excluded; 55% if all "possible" infectious cases excluded). This is a high proportion compared with previous studies [1], and higher than that identified using *International Classification of Diseases*–coded hospitalization data [6]. Prospective case ascertainment with detailed case review and categorization has contributed to this, as has including young infants (aged <6 months) where an infectious etiology is most common. A prospective UK study of all-age encephalitis that used similar methods had a similarly high proportion of cases with a putative cause [5]. Additional contributors are the contemporary availability of molecular testing (especially for viruses) and increased awareness of antibody mediated encephalitides. Despite

this, 1 in 5 cases of childhood encephalitis had no cause identified. Even in this study, where diagnostic guidelines specific to Australia were published and disseminated, they appear to have been incompletely applied [14]. Optimal implementation of such guidelines may further reduce the proportion with unknown cause. However, we also observed several cases where extensive diagnostic testing was performed but no diagnosis made; new causes may be found, although inadequate sensitivity of current tests cannot be ruled out. A further challenge is that there were no clear clinical features or risk factors to differentiate these cases from those cases with known causes. New approaches to diagnosis in childhood encephalitis are required including the use of next-generation sequencing that appears promising [30, 31].

A further insight arising from this cohort is the interaction of infectious and immune-mediated etiologies. Two cases of post-HSV encephalitis, anti-NMDAR encephalitis were observed, an emerging syndrome that is changing paradigms of infection-mediated autoimmunity [32]. We offer an estimate that anti-NMDAR occurs in 10% of childhood HSV encephalitis (15% if neonatal disease excluded), which is somewhat lower than that in a recent study from Spain [33]. Here, cases were not systematically tested for antibodies but were found on the basis of clinical relapse. Furthermore, we observed serological evidence for recent infection among 14% of ADEM cases. ADEM is often associated with infection and frequently denoted as a "postinfectious" syndrome, although its pathogenesis remains elusive [34]. It is the most frequent cause of childhood encephalitis and appears to be increasing in frequency [6, 7]. Additionally, the median age of children with immune-mediated encephalitis was significantly older than those with infectious causes. The interaction between age, immune function, and infectious exposures needs greater attention to advance our understanding of the pathogenesis of severe CNS inflammation [35].

We have shown that short-term outcome at discharge, including death, was significantly associated with cause. Severe brain injury may result from both true encephalitis (eg, HSV) and infection-associated encephalopathy (eg, influenza). The contribution of influenza emphasizes that multiple pathways of pathogenesis are important in childhood encephalitis syndrome; both pathological encephalitis and severe encephalopathy contribute to the burden of disease [36]. There is a need to better define the pathogenesis of these heterogeneous diseases to improve targeting of available therapies. Influenza was independently associated with death or neurological morbidity, also emphasizing a need for enhanced influenza prevention efforts among children.

Our study has considerable strengths. The prospective, active case ascertainment ensured a high likelihood that we have not missed any cases at participating sites. Equally, demographic and hospitalization data were complete. Waiver of consent ensured that cases resulting in death were included. All diagnostic testing data were pursued and fully reviewed by the expert panel. However, we acknowledge limitations in some collected data because clinical assessment and diagnostic testing were at the discretion of attending clinicians and detailed neurological assessment was variable, in part because of challenges in evaluating the high proportion of very young children. A further potential limitation is that among infectious causes, we have included cases with "possible" causation when aggregating the etiological spectrum. The expert panel rigorously applied the Granerod et al criteria when categorizing cases [11]; however, we have included "possible" causes because these criteria may underestimate the causative role of certain pathogens. In the case of enteroviruses, there is growing evidence showing the limited sensitivity of CSF nucleic acid detection in neurotropic enteroviruses including EVA71 and EVD68 [37, 38]. One study has assigned "probable" causation when enterovirus was identified in 2 sites concurrently (respiratory and gastrointestinal) to recognize its strength of association during encephalitis (occurred in 5 of 12 ACE possible enterovirus cases) [39]. Furthermore, we believe the Granerod et al definitions give insufficient weight to causes of infection associated encephalopathy where the CNS syndrome has arisen from brain inflammation triggered by an infection elsewhere (indirect pathogenesis). In the case of influenza, during seasonal epidemics where a clinicoradiological syndrome such as acute necrotizing encephalopathy is observed in association with influenza [36], many would consider its causative role to be at least "probable" [40]. This applies to the majority of influenza-associated encephalitis cases described here. Other childhood infections for which this is an important consideration include rotavirus, norovirus, RSV, and HHV-6 [41, 42]. In contrast, the detection of β- and γ-herpesviruses (EBV, CMV, HHV-6) by PCR in CSF may overestimate their significance [43]. This is particularly the case where timely serology is lacking, and for HHV-6 where chromosomal integration is not excluded [11]. One case each of "probable" EBV encephalitis and "possible" HHV-6 encephalitis were subject to these limitations. A further important controversy surrounds the attribution of *M. pneumoniae* as a cause partly because of inherent limitations with available diagnostic tests [19, 44, 45]. Here, all cases were diagnosed serologically, did not have alternative causes, and did not have imaging consistent with ADEM as per Granerod et al. We acknowledge that the reporting of "possible" causes is most problematic when >1 pathogen was identified ("mixed" infectious encephalitis in Table 1).

A further limitation is that a definitive, long-term outcome is yet to be characterized in this cohort. Twenty-seven percent of children showed neurodisability at discharge using the GOS. The GOS is validated for use in traumatic brain injury and was used for simplicity, although we acknowledge that for encephalitis it is a nonvalidated and crude measure. We therefore chose

to analyze it as a binary outcome measure only. It cannot be considered predictive of long-term outcome. We note that for both anti-NMDAR and ADEM, the short-term outcomes reported here likely do not correlate with the expected medium-term recovery in many cases [34, 46]. A recent systematic review of the long-term outcome of childhood infectious encephalitis showed that incomplete recovery was reported in 42.0% of cases (95% CI, 32%–53%; pooled estimate) [47]. The short-term outcomes reported likely underestimate the overall neurodevelopmental sequelae in this cohort.

CONCLUSIONS

This is one of the largest and most rigorous studies of childhood encephalitis. The most common specific causes were enteroviruses, parechovirus, HSV, influenza, *M. pneumoniae*, ADEM, and anti-NMDAR; one-fifth of cases had an unknown cause. This severe disease continues to cause death in 1 in 20 affected children, and results in considerable neurological morbidity among survivors.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C. A. J., R. B., E. J. E., and R. C. D. conceptualized the Australian Childhood Encephalitis (ACE) study and drafted initial surveillance protocols. P. N. B. and C. A. J. drafted the final ACE surveillance study protocol and designed the case report form, and P. N. B. trained the Paediatric Active Enhanced Disease Surveillance (PAEDS) nurses. C. A. J., P. N. B., R. C. D., and R. B. were members of the ACE study expert panel. P. N. B. and R. C. D. reviewed neuroimaging on selected cases. K. M., C. C. B., N. C., J. E. C., and H. M. are the PAEDS site leads for the ACE study. P. N. B., C. A. J., R. C. D., and R. B. conceptualized this analysis. P. N. B. further reviewed all the cases for the combined analysis, pooled the data, performed the analysis, and drafted the initial manuscript. All authors reviewed, revised, and approved the final manuscript as submitted.

Acknowledgments. The authors thank the PAEDS Network surveillance nurses: Jocelynne McRae, Jenny Murphy, Laura Rost, Sharon Tan, Helen Knight, Kathryn Meredith, Natalie McLaren, Nicole Dinsmore, Gemma Saravanos, Alissa McMinn, Donna Armstrong, Christine Heath, Caroline Finucane, and Sonia Dougherty, as well as laboratory and medical records staff at each site. The authors thank the other PAEDS investigators: Associate Professor Nicholas Wood and Professor Peter McIntyre (The Children's Hospital at Westmead); Professor Jim Buttery (Monash Children's and Royal Children's Hospital, Melbourne); Dr Anne Kynaston (Queensland Children's Hospital, Brisbane); Professor Jim Gold (Women's and Children's Hospital, Adelaide); and Associate Professor Peter Richmond (Princess Margaret Hospital, Perth). The authors also thank Professor Alison Kesson (ACE study investigator).

Financial support. This work was supported by the Australian Commonwealth Department of Health and the National Health and Medical Research Council (NHMRC) including through the NHMRC Centre for Research Excellence in Critical Infections (Grant [GNT] 1001021) to C. A. J. and R. B.; and the NHMRC Centre for Research Excellence in Emerging Infectious Diseases to C. A. J. (GNT1102692). P. N. B. was supported by an NHMRC postgraduate fellowship (GNT1074547) and Early Career Fellowship (GNT1145817), the Royal Australasian College of Physicians, and the Arkadia Fund (Norah Therese Hayes Ratcliffe PhD lectureship). C. C. B. and H. M. were supported by NHMRC career development fellowships (GNT 1111596 and GNT1084951, respectively). C. A. J. has received grants from the University of Sydney Marie Bashir Institute, for CNS I3 node support. R. B., R. C. D., and E. J. E. were supported by NHMRC Practitioner Fellowships (GNT1110891, GNT1059157, and GNT1021480, respectively). PAEDS is funded by an NHMRC Partnership Grant (GNT1113851) and by the Australian Government Department of Health and state health departments.

Potential conflicts of interest. H. M. has been an investigator on clinical trials of investigational vaccines sponsored by industry and has received grants for investigator-led research from GSK, Novartis, Pfizer, and Seqiris. Her institution also receives funding from industry (GSK, Novavax, Pfizer) to conduct clinical trials of investigational vaccines. R. B. works with several manufacturers of influenza vaccines in an advisory capacity, as a researcher on vaccines and as presenter of academic information at conferences, and also occasionally as an advisory board member. He receives support to travel and attend such conferences and meetings from, eg, BioCSL/Seqiris, GSK, Sanofi, Novartis, and Medimmune/AstraZeneca; on occasions that he also receives an honorarium, it is paid direct to his institution. Any funding received is directed to a research account at the Children's Hospital at Westmead and is not personally accepted by R. B. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Britton PN, Dale RC, Booy R, Jones CA. Acute encephalitis in children: progress and priorities from an Australasian perspective. J Paediatr Child Health **2015**; 51:147–58.
2. Easton A. Encephalitis: raising awareness and collaborating in research. Lancet Neurol **2016**; 15:353.
3. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis **2006**; 43:1565–77.
4. Mailles A, Stahl JP; Steering Committee and Investigators Group. Infectious encephalitis in France in 2007: a national prospective study. Clin Infect Dis **2009**; 49:1838–47.
5. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Erratum in Lancet Infect Dis 2011; 11:79. Lancet Infect Dis **2010**; 10:835–44.
6. Britton PN, Khoury L, Booy R, Wood N, Jones CA. Encephalitis in Australian children: contemporary trends in hospitalisation. Arch Dis Child **2016**; 101:51–6.
7. Iro MA, Sadarangani M, Goldacre R, Nickless A, Pollard AJ, Goldacre MJ. 30-year trends in admission rates for encephalitis in children in England and effect of improved diagnostics and measles-mumps-rubella vaccination: a population-based observational study. Lancet Infect Dis **2017**; 17:422–30.
8. Bagdure D, Custer JW, Rao S, et al. Hospitalized children with encephalitis in the United States: a pediatric health information system database study. Pediatr Neurol **2016**; 61:58–62.
9. Zurynski Y, McIntyre P, Booy R, Elliott EJ; PAEDS Investigators Group. Paediatric active enhanced disease surveillance: a new surveillance system for Australia. J Paediatr Child Health **2013**; 49:588–94.
10. Britton PN, Dale RC, Elliott E, et al. Pilot surveillance for childhood encephalitis in Australia using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. Epidemiol Infect **2016**; 1–11.
11. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect **2010**; 138:783–800.
12. Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine **2007**; 25:5771–92.
13. Dale RC, Brilot F, Banwell B. Pediatric central nervous system inflammatory demyelination: acute disseminated encephalomyelitis, clinically isolated syndromes, neuromyelitis optica, and multiple sclerosis. Curr Opin Neurol **2009**; 22:233–40.
14. Britton PN, Eastwood K, Paterson B, et al; Australasian Society of Infectious Diseases (ASID); Australasian College of Emergency Medicine (ACEM); Australian and New Zealand Association of Neurologists (ANZAN); Public Health Association of Australia (PHAA). Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J **2015**; 45:563–76.

15. Zander A, Britton PN, Navin T, Horsley E, Tobin S, McAnulty JM. An outbreak of enterovirus 71 in metropolitan Sydney: enhanced surveillance and lessons learnt. Med J Aust **2014**; 201:663–6.
16. Cumming G, Khatami A, McMullan BJ, et al. Parechovirus genotype 3 outbreak among infants, New South Wales, Australia, 2013–2014. Emerg Infect Dis **2015**; 21:1144–52.
17. Britton PN, Jones CA, Macartney K, Cheng AC. Parechovirus: an important emerging infection in young infants. Med J Aust **2018**; 208:365–9.
18. Britton PN, Blyth CC, Macartney K, et al. The spectrum and burden of influenza-associated neurological disease in children: combined encephalitis and influenza sentinel site surveillance from Australia, 2013–2015. Clin Infect Dis **2017**; 65:653–60.
19. Britton PN, Bag SK, Booy R, et al. Probable epidemic *Mycoplasma pneumoniae* disease activity in metropolitan Sydney, 2015: combining surveillance data to cross-validate signal detection. Commun Dis Intell Q Rep **2017**; 41:E295–307.
20. Joseph L, May M, Thomas M, et al. Human parechovirus 3 in infants: expanding our knowledge of adverse outcomes. Pediatr Infect Dis J **2019**; 38:1–5. doi:10.1097/INF.0000000000002136.
21. Lewis P, Glaser CA. Encephalitis. Pediatr Rev **2005**; 26:353–63.
22. Zurynski YA, McRae JE, Quinn HE, Wood NJ, Macartney KK. Paediatric active enhanced disease surveillance inaugural annual report, 2014. Commun Dis Intell Q Rep **2016**; 40:E391–400.
23. Pillai SC, Hacohen Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. Pediatrics **2015**; 135:e974–84.
24. Le VT, Phan TQ, Do QH, et al. Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. PLoS Negl Trop Dis **2010**; 4:e854.
25. Ho Dang Trung N, Le Thi Phuong T, Wolbers M, et al; VIZIONS CNS Infection Network. Aetiologies of central nervous system infection in Viet Nam: a prospective provincial hospital-based descriptive surveillance study. PLoS One **2012**; 7:e37825.
26. Fowler A, Stödberg T, Eriksson M, Wickström R. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. Eur J Paediatr Neurol **2008**; 12:484–90.
27. Heywood AE, Wang H, Macartney KK, McIntyre P. Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study. Bull World Health Organ **2014**; 92:593–604.
28. Huppatz C, Gawarikar Y, Levi C, et al. Should there be a standardised approach to the diagnostic workup of suspected adult encephalitis? A case series from Australia. BMC Infect Dis **2010**; 10:353.
29. Elstein AS, Schwartz A, Schwarz A. Clinical problem solving and diagnostic decision making: selective review of the cognitive literature. BMJ **2002**; 324:729–32.
30. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. N Engl J Med **2014**; 370:2408–17.
31. Brown JR, Morfopoulou S, Hubb J, et al. Astrovirus VA1/HMO-C: an increasingly recognized neurotropic pathogen in immunocompromised patients. Clin Infect Dis **2015**; 60:881–8.
32. Armangue T, Leypoldt F, Málaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol **2014**; 75:317–23.
33. Armangue T, Spatola M, Vlagea A, et al; Spanish Herpes Simplex Encephalitis Study Group. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol **2018**; 17:760–72.
34. Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology **2007**; 68:S23–36.
35. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev **2016**; 15:307–24.
36. Britton PN, Blyth CC, Macartney K, et al. The spectrum and burden of influenza-associated neurological disease in children: combined encephalitis and influenza sentinel site surveillance from Australia, 2013–2015. Clin Infect Dis **2017**; 65:653–60.
37. Pérez-Vélez CM, Anderson MS, Robinson CC, et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. Clin Infect Dis **2007**; 45:950–7.
38. Aliabadi N, Messacar K, Pastula DM, et al. Enterovirus D68 infection in children with acute flaccid myelitis, Colorado, USA, 2014. Emerg Infect Dis **2016**; 22:1387–94.
39. Le VT, Phan TQ, Do QH, et al. Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. PLoS Negl Trop Dis **2010**; 4:e854.
40. Goenka A, Michael BD, Ledger E, et al. Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. Clin Infect Dis **2014**; 58:775–84.
41. Sweetman LL, Ng YT, Butler IJ, Bodensteiner JB. Neurologic complications associated with respiratory syncytial virus. Pediatr Neurol **2005**; 32:307–10.
42. Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev **2012**; 34:337–43.
43. Britton PN, Jones CA. Central nervous system herpesvirus infections. Paediatr Child Health **2014**; 24:248–54.
44. Narita M. Pathogenesis of neurologic manifestations of *Mycoplasma pneumoniae* infection. Pediatr Neurol **2009**; 41:159–66.
45. Christie LJ, Honarmand S, Talkington DF, et al. Pediatric encephalitis: what is the role of *Mycoplasma pneumoniae*? Pediatrics **2007**; 120:305–13.
46. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol **2013**; 12:157–65.
47. Khandaker G, Jung J, Britton PN, King C, Yin JK, Jones CA. Long-term outcomes of infective encephalitis in children: a systematic review and meta-analysis. Dev Med Child Neurol **2016**; 58:1108–15.